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REVIEW

Existing Data Sources in Clinical Epidemiology: Database of Community Acquired Infections Requiring Hospital Referral in Eastern Denmark (DCAIED) 2018–2021

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Abstract: Infectious diseases are major health care challenges globally and a prevalent cause of admission to emergency departments. Epidemiologic characteristics and outcomes based on population level data are limited. The Database of Community Acquired Infections in Eastern Denmark (DCAIED) 2018–2021 was established with the aim to explore and estimate the population characteristics, and outcomes of patients suffering from community acquired infections at the emergency departments in the Capital Region and the Zealand Region of Denmark using data from electronic medical records. Adult patients (≥18 years) presenting to the emergency department with suspected or confirmed infection are included in the cohort. Presence of sepsis and organ failure are assessed using modified criteria from the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). During the inclusion period from January 2018 to January 2022, 2,241,652 adult emergency department visits have been registered. Of these, 451,825 were unique encounters of which 60,316 fulfilled criteria of suspected infection and 28,472 fulfilled sepsis criteria and 8,027 were defined as septic shock. The database covers the entire Capital and Zealand Region of Denmark with an uptake area of 2.6 million inhabitants and includes demographic, laboratory and outcome indicators, with complete follow-up. The database is well-suited for epidemiological research for future national and international collaborations.

Keywords: emergency department, infectious diseases, sepsis, shock, database, epidemiology, community acquired

Introduction

Globally, infectious diseases are major causes of morbidity and mortality, of which sepsis accounts for the majority of deaths.[1] Lower respiratory infections remain one of the leading causes of death in both high- and low-income countries.[1,2] Sepsis, a subset of underlying infection with the presence of organ failure, is a syndromic illness associated with high morbidity and mortality.[3,4] Estimated global sepsis cases are 48.9 million per year accounting for up to 20% of global deaths.[2]

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A Danish single-center population-based study in 2015 suggested an incidence of 731/100,000 person-years at risk of community-acquired sepsis of any severity with an observed 30-day mortality of 14%.[5,6] Accordingly, another prospective single-center Danish study from 2021 found an incidence of sepsis (based on Sequential Organ Failure Assessment (SOFA) score of ≥2 at admission) 721/100,000 person-years and a 28-day mortality of 13.8%.[7] However, sepsis is likely underreported in Denmark.[8] With an aging and increasingly comorbid population presenting to the emergency department (ED), the proportion of patients suffering from infectious diseases requiring hospital referral and treatment will likely rise. To characterize the burden of disease and identify populations of interest for future prospective studies on infectious diseases and sepsis in the ED, large-scale epidemiological studies are warranted.

The purpose of this database is to establish an infrastructure for epidemiological research as well as assessment of the treatment and care of community acquired infections, sepsis and septic shock among patients with a primary contact to the ED.

Perspectives on Infection and Sepsis Definitions

Sepsis has been described since antiquity.[9] As a syndrome rather than a disease, clinical definitions of sepsis have been proposed by combining clinical and laboratory variables. Consensus definitions have been endorsed at international conferences held in 1991, 2001, and 2016 (Table 1).[10–12] The initial sepsis definition was defined as a systemic inflammatory response syndrome (SIRS) to infection in 1991[10] but revised in 2001 to incorporate organ damage thresholds but without changing the sepsis definition.[11] Since then, the paradigm of sepsis pathophysiology has changed. SIRS was in 2016 ascertained an outdated paradigm with poor specificity and was abandoned as a definition of sepsis.[12] Subsequently, sepsis was defined a life-threatening organ dysfunction caused by a dysregulated host response to infection.[12] In this

Table 1 Definitions of Sepsis

Sepsis 1 (1991)[10] Systemic inflammatory response syndrome (SIRS): systemic inflammatory response to a variety of severe clinical insults: Temperature >38°C or <36°C; heart rate >90 beats per min; respiratory rate >20 breaths per min or $PaCO_2$ <32 mmHg; and white blood cell count >12,000/cu mm, <4000/cu mm, or >10% immature (band) forms Sepsis is a systemic response to infection, manifested by two or more of the SIRS criteria as a result of infection. Severe sepsis: Sepsis associated with organ dysfunction, hypoperfusion, or hypotension; hypoperfusion and perfusion abnormalities may include, but not limited to, lactic acidosis, oliguria, or an acute alteration in mental status or hypotension. Septic shock: Sepsis-induced, with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but not limited to, lactic acidosis, oliguria, or an acute alteration in mental status; patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.
Sepsis 2 (2001)[11] Infection: Documented or suspected and some of the following: **General parameters:** Fever (core temperature >38.3°C); hypothermia (core temperature <36°C); heart rate >90 beats per min or >2 SD above the normal value for age; tachypnea: respiratory rate >30 breaths per min; altered mental status; significant edema or positive fluid balance (>20 mL/kg−1 over 24 h). Hyperglycemia (plasma glucose >110 mg/dL−1 or 7.7 mML^{-1}) in the absence of diabetes **Inflammatory parameters:** Leukocytosis (white blood cell count >12,000/μL); leukopenia (white blood cell count <4000/μL); normal white blood cell count with >10% immature forms; plasma C-reactive protein >2 SD above the normal value; and plasma procalcitonin >2 SD above the normal value **Hemodynamic parameters:** Arterial hypotension (systolic blood pressure <90 mmHg, MAP <70 mmHg, or a systolic blood pressure decrease >40 mmHg in adults or <2 SD below normal for age, mixed venous oxygen saturation >70%, cardiac index >3.5 L min^{-1} m^{-2}) **Organ dysfunction parameters**: Arterial hypoxemia (PaO_2/FIO_2 <300); acute oliguria (urine output <0.5 mL/kg^{-1} h^{-1} or 45 mM L^{-1} for at least 2 h); creatinine increase ⩾0.5 mg/dL^{-1}; coagulation abnormalities (international normalized ratio >1.5 or activated partial thromboplastin time >60 s); ileus (absent bowel sounds); thrombocytopenia (platelet count <100,000 μL^{-1}) Hyperbilirubinemia (plasma total bilirubin >4 mg/dL^{-1} or 70 mmol L^{-1}) **Tissue perfusion parameters:** Hyperlactatemia (>3 mmol/L^{-1}); decreased capillary refill or mottling

(*Continued*)

Table 1 (Continued).

Sepsis 3 (2016)[12]
Sepsis is a life-threatening organ dysfunction caused by dysregulated host response to infection.
Clinical criteria for sepsis:
Suspected or documented infection and an acute increase of ≧2 SOFA points
The task force considered that positive qSOFA (quick SOFA) criteria should also prompt consideration of possible infection in patients not previously recognized as infected.
qSOFA criteria:
Altered mental status (GCS score <15)
Systolic blood pressure <100 mmHg
Respiratory rate >22 breaths per min
Septic shock is defined as a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality.
Septic shock can be identified with a clinical construct of sepsis with persisting hypotension, requiring vasopressor therapy to elevate MAP ≥65 mmHg and lactate >2 mmol/L^{-1} (18 mg/dL^{-1}) despite adequate fluid resuscitation

definition SIRS was eliminated due to its low sensitivity and specificity in discriminating sepsis and noncomplicated infection. Organ dysfunction was defined as an acute increase in the total Sequential Organ Failure Assessment (SOFA) score of at least two points secondary to the infection which is associated with an in-hospital mortality of >10% (Table 2).[12] Septic shock is a subset of sepsis characterized by circulatory failure, and carries a substantially increased risk of death compared to sepsis.[12–14] To early identification of patients with suspected infection outside of critical care units and likely to develop sepsis, a new bedside tool with almost similar predictive validity for in-hospital mortality as SOFA outside the Intensive Care Unit (ICU), the quick Sequential Organ Failure Assessment (qSOFA) was introduced.[3] The qSOFA score consists of three variables based on vital parameters (systolic blood pressure, respiratory frequency) and a clinical judgment of cerebral status (Glasgow Coma Score). However, qSOFA had lower validity as a measure of organ dysfunction.[3] Therefore, in the 2021 updated international guidelines for the management of sepsis and septic shock, it was recommended against using qSOFA compared to SIRS, National Early Warning Score (NEWS), or Modified Early Warning Score (MEWS) as a single screening tool for sepsis or septic shock.[15]

Population-based epidemiological studies of community acquired infections, sepsis and septic shock are scarce and the few studies available have found differences in estimates likely reflecting differences in case definitions and quality of data.[16] To determine whether an infection is present or not, is a clinical challenge. Furthermore, with the lack of a gold standard for accurate diagnosis and a heterogenous clinical presentation of sepsis, reported sepsis outcomes are prone to be biased. Table 3 provides an overview of the major epidemiological studies conducted during the past three decades.

Materials and Methods

Aim of the Database

The purpose of the database is to conduct epidemiological research and to examine the treatment and care of community acquired infections, sepsis and septic shock.

Study Population and Setting

The database comprises all adult ED visits of patients (age ≥18 years) of the Capital and Zealand Regions of Denmark from January 1, 2018 to January 1, 2022. The EDs provide 24-h acute emergency care for 2.6 million inhabitants with approximately 803,983 annual adult contacts and 257,238 annual admissions.[39,40] All adults living in the catchment area are eligible for inclusion at the time of presentation to the EDs. In Denmark, all residents have access to free health care. Every resident is assigned a unique 10-digit personal civil registration number (CPR-number). This unique CPR-number enables accurate linkage between the Danish national registers[41] and true population-based studies are hereby possible.[41] Data on municipality of residence, migration-, and vital status, and date of birth are retrieved from The Danish Civil Registration System (DCRS) and linked to other registries and databases using the unique CPR-number.[41]

Table 2 Sequential Organ Failure Assessment (SOFA) score[12]

SOFA SCORE	Central Nervous System	Cardiovascular System	Respiratory System	Coagulation	Liver	Renal Function
Score	**Glasgow Coma Scale**	**Mean Arterial Pressure OR Administration of Vasopressors Required**	**PaO_2/FiO_2 [mmHg (kPa)]**	**Platelets×$10^3/\mu L$**	**Bilirubin (mg/dl) [μmol/L]**	**Creatinine (mg/dl) [μmol/L] (or Urine Output)**
0	15	MAP ≥70 mmHg	≥400 (53.3)	≥150	< 1.2 [<20]	<1.2 [<110]
1	13–14	MAP <70 mmHg	<400 (53.3)	<150	1.2–1.9 [20–32]	1.2–1.9 [110–170]
2	10–12	Dopamine ≤5 μg/kg/min or dobutamine (any dose)	<300 (40)	<100	2.0–5.9 [33–101]	2.0–3.4 [171–299]
3	6–9	Dopamine >5 μg/kg/min OR epinephrine ≤ 0.1 μg/kg/min OR norepinephrine ≤0.1 μg/kg/min	<200 (26.7) and mechanically ventilated including CPAP	<50	6.0–11.9 [102–204]	3.5–4.9 [300–440] (or <500 mL/day)
4	< 6	Dopamine > μg/kg/min OR epinephrine >0.1 μg/kg/min OR norepinephrine >0.1 μg/kg/min	<100 (13.3) and mechanically ventilated including CPAP	<20	> 12.0 [>204]	>5.0 [>440] (or <200 mL/day)

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Table 3 Major Epidemiological Studies Reporting Sepsis Outcomes and Trends

Study	Country	Study Period	Criteria Used for Diagnosis	Setting/ Population	Data Source	Incidence	Mortality
CDC, JAMA, 1990[17]	USA	1979–1987	Septicemia based on hospital discharge diagnoses	Nationwide	Administrative data: NHDS	73.6 to 175.9 per 100,000 (139% relative increase)	NA
Angus et al, Crit Care Med, 2001[18]	USA	1995	ICD-9-CM discharge codes	Acute hospitalization/ Estimated nationwide	Administrative data: HCFA	300.0 per 100,000 population	In-hospital mortality: 28.6%
Martin et al, NEJM 2003[19]	USA	1979–2000	ICD-9-CM discharge codes	Hospitalization/ Estimated nationwide	Administrative data: NHDS	82.7 to 240.4 per 100,000 population (8.7%, Estimated increase per year)	27.8% to 17.9%
Flaatten, Crit Care Lond Engl. 2004[20]	Norway	1999	ICD-10 discharge codes	Hospitalized/ Nationwide	Administrative data: NPR	Sepsis: 149 per 100,000 population, Severe sepsis: 56 per 100,000 population	In-hospital mortality: Sepsis: 13.9%, Severe sepsis: 27%
Finfer et al, Intensive Care Med 2004[21]	Australian and New Zealand	1999	SEPSIS-1/PROWESS	ICU	Clinical Database	Severe Sepsis: 77 per 100,000 population (Estimated)	28-day mortality: 32.4%
Brun-Buisson et al, Intensive Care Med. 2004[22]	France	2001	Sepsis-1	ICU/Estimated nationwide	Clinical Database	Severe Sepsis: 95 per 100,000 population (Estimated)	30-day mortality: 35%
Esper et al, Crit Care Med, 2006[23]	USA	1979–2003	ICD-9-CM discharge codes	Hospitalization/ Estimated nationwide	Administrative data: NHDS	Sepsis: 82.7 to 275.4 per 100,000 population, Severe sepsis: NA	In-hospital mortality: 20.3%
Harrison et al, Crit. Care Lond. Engl. 2006[24]	England, Wales, and Northern Ireland	1996–2004	PROWESS	ICU/Estimated nationwide	Clinical Database: ICNARC	Severe Sepsis 46 to 66 per 100,000 population (Estimated)	In-hospital mortality: 48.3–44.7% (Estimated decrease)
Dombrovskiy et al, Crit Care Med 2007[25]	USA	1993–2003	ICD-9-CM	Acute hospitalization/ Estimated nationwide	Administrative data: NIS	Severe sepsis: 65.0 to 135.0 per 100,000 population (Estimated increase)	In-hospital mortality: 45.8% to 37.8% (Estimated decrease)
Wang et al, Crit Care Med 2007[26]	USA	2001–2004	ICD-9-CM discharge codes	ED/Estimated nationwide	Administrative data: NHAMCS	Severe Sepsis: 194.0 per 100,000 population	NA
Karlsson et al, Intensive Care Med. 2007[27]	Finland	2004–2005	Sepsis-1	ICU/ Nationwide	Clinical Database	Severe Sepsis: 69.0 per 100,000 population	ICU mortality: 15.5% In-hospital Mortality: 28.3%

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Table 3 (Continued).

Study	Country	Study Period	Criteria Used for Diagnosis	Setting/ Population	Data Source	Incidence	Mortality
Wilhelms et al, Crit Care Med 2010[28]	Sweden	1987–2005	ICD-9/10	Nationwide	Administrative data: SHDR	Severe Sepsis: 10.0–35.0 per 100,000 population, 3.0–13.0 per 100,000 population, and 26.0–43.0 per 100,000 population (depending on method used, Estimated)	Severe Sepsis: In-hospital mortality: 22.1%, 22.4%, and 29.2% (depending on method used)
Kumar et al, Chest 2011[29]	USA	2000–2007	ICD-9-CM	Acute hospitalization/ Estimated nationwide	Administrative data: NIS	Severe Sepsis: 143 to 343 per 100,000 population (Estimated increase)	In-hospital mortality: 39% to 27% (Estimated decrease)
Lagu et al, Crit Care Med 2012[30]	USA	2003–2007	ICD-9-CM	Acute hospitalization/ Estimated nationwide	Administrative data: NIS	Severe Sepsis: 303 to 1074 per 100,000 population (depending on method used, Estimated)	In-hospital mortality: 14.0%
Gaieski et al, Crit Care Med 2013[31]	USA	2004–2009	ICD-9-CM	Acute hospitalization/ Estimated nationwide	Administrative data: NIS	Severe Sepsis: 300 to 1031 per 100,000 population (depending on method used, Estimated)	In-hospital mortality: 14.7% and 29.9% (depending on method used), overall estimated decrease
Kaukonen et al, JAMA 2014[32]	Australia and New Zealand	2000–2012	Sepsis-1	ICU	Clinical Database: ANZICS	NA	Severe sepsis with and without shock (In-hospital mortality): 35.0% to 18.4%, (estimated decrease: 1.3% per year)
Bouza et al, BMC Infect Dis 2014[33]	Spain	2006–2011	ICD-9-CM	Nationwide	Administrative data: NMBD	Severe sepsis: 63.9 to 105.5 per 100,000 population (increase).	In-hospital mortality rate: 32.1 to 45.3 cases per 100,000 (decrease)
Kadri et al, Chest 2017[34]	USA	2005–2014	Clinical surveillance definition (concurrent vasopressors, blood cultures, and antibiotics) vs ICD-9-CM discharge codes	Acute hospitalization/ Estimated nationwide	Clinical Database/EHR	Septic shock (Clinical Data): 1280 to 1860 per 100,000 population (average, 4.9% increase per year) Septic shock (ICD-9-CM): 670 to 1930 per 100,000 (19.8% increase per year)	Septic shock (in-hospital mortality, Clinical Data): 54.9% to 50.7% (estimated decrease), 48% to 39.3 Septic shock (in-hospital mortality, ICD-9-CM): 48.0% to 39.3% (estimated decrease)
Lee et al, J Infect 2017[35]	Taiwan	2002–2012	ICD-9-CM	Acute hospitalization/ Nationwide	Administrative data: NHICD	Sepsis (severe sepsis and septic shock): 637.8 to 772.1 per 100,000 (relative increase: 21.1%)	Sepsis (In-hospital mortality): 23.3% to 17.9% (decrease), Septic shock (In-hospital mortality): 40.5% to 33.2% (decrease)

Rhee et al, JAMA 2017[4]	USA	2009–2014	Sepsis-3 (Clinical Criteria) vs ICD-9-CM discharge codes	ED/Estimated nationwide	Clinical Database/EHR	Sepsis (Clinical criteria): 6% (+0.6% relative change per year, not significant), Sepsis/Severe Sepsis/Septic Shock (ICD-9-CM): (+7.3% per year to +10.3% per year).	Sepsis (In-hospital mortality, clinical criteria): 15.6% (3.3% decrease per year) Sepsis (In-hospital mortality, ICD-9-CM): (7.0% decrease per year)
Rubens et al, J Intensive Care Med 2018[36]	USA	2005–2014	ICD-9-CM	ED/Estimated nationwide	Administrative data: NIS	541,694 to 1,338,905 (124% relative increase)	31.9% to 17.1% (46% relative decrease)
Fleischmann-Struzek et al, Crit Care Med 2018[37]	Germany	2010–2015	ICD-10-GM	Nationwide	Administrative data:	Sepsis: 280 to 370 per 100,000 population (5.7% increase per year), Severe sepsis: 108 to 158 per 100,000 population (7.9% increase per year)	Severe Sepsis/Septic shock: In-hospital mortality: 47.8 to 41.7%, decrease.
Oh SY et al, Crit Care Med 2019[38]	Korea	2007–2016	ICD-10	Nationwide	Administrative data: NHIS	173.8 to 233.6 per 100,000 population (increase)	30.9 to 22.6% (decrease)
Rudd et al, Lancet 2020[2]	Global	1990–2017	ICD-9 and ICD-10	Global estimates	Administrative data: GBD	Sepsis: 1074.7 to 677.5 per 100,000 population (Estimated decrease of 37.0%)	Sepsis (overall mortality): 148.1 per 100,000 population, (relative decrease 29.7%)

Note: Epidemiological studies of sepsis, severe sepsis and septic shock.

Abbreviations: ANZICS, Australian and New Zealand Intensive Care Society adult ICU patient database; GBD, Global Burden of Diseases, Injuries, and Risk Factors Study; ED, Emergency Department; EHR, electronic health record; HCFA, health care financing administration (USA); ICD-9-CM, Clinical Modification of the International Statistical Classification of Diseases – Ninth Revision; ICD-10, International Statistical Classification of Diseases – Tenth Revision; ICD-10-GM, ICD-10 German Modification; ICU, intensive care unit; ICNARC, Intensive Care National Audit & Research Centre; NMBD, national minimum basic data set (Spain); NA, not available; NHAMCS, National Hospital Ambulatory Medical Care Survey (USA); NHICD, National Health Insurance claims database (Taiwan); NIS, nationwide inpatient sample (USA); NHDS, National Hospital Discharge Survey (USA); NHIS, National Health Insurance Service (Korea); NPR, Norwegian Patient Registry; PROWESS, Protein C Worldwide Evaluation in Severe Sepsis (study of drotrecogin alfa); SHDR, Swedish Hospital Discharge Database.

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The Danish National Patient Registry (DNPR) cover all unique inpatient and outpatient clinical contacts at hospitals in Denmark collecting data regarding dates of admission, discharge, admitting departments and all primary and secondary discharge diagnoses (ICD-10 code system)[42] from hospitals (except psychiatric departments and hospitals).[43] Information regarding the population of persons living in the hospitals catchment area is available from Statistics Denmark website.[44]

The advantages and use of Danish registries in epidemiological studies as well as details of the Danish health care system has been described elsewhere.[45] Patients in Denmark, who are hospitalized acutely, are admitted through the ED of a public hospital, either by their own initiative, referred by general practitioners, or directly by the emergency ambulance service. Patients experiencing more severe infections requiring acute treatment are often treated initially in the ED, including administration of antibiotics. Patients with more severe organ failure (respiratory failure, circulatory failure, etc) are treated in ICU.

Infection, Sepsis and Septic Shock Definitions

In this cohort, suspected infection is adapted and modified from the US Centers for Disease Control and Prevention and defined clinically as a patient admitted to an ED who has any specimens obtained for culture from any anatomic site (irrespective of the result) and the administration of any antimicrobial agent starting within 24 h after arrival to the ED (Table 4).[46] Accordingly, the sepsis case definition is adapted and modified from the US Centers for Disease Control and Prevention, and The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).[12,46] Septic shock is defined by the need for vasopressor to maintain mean arterial pressure ≥65 mmHg or a serum lactate ≥18 mg/L (2 mmol/L).[47] See Table 4 for complete definitions.

Data Collection and Variables

Database Population

Since March 18, 2017 all patients records from the EDs and hospitals in the Capital and Zealand Region of Denmark are registered and available as electronic medical records (EMR) in *Sundhedsplatforme* provided by EPIC©.[48] By electronic screening and the unique CPR-number it is possible to identify and retrieve information on all patients' unique variables including demographic variables (municipality of residence, migration, and vital status, and date of birth), vital parameters, laboratory values, primary and secondary diagnoses, medication status at admission, and medication administered during hospitalization. As of January 1, 2022, 2,241,652 adult ED cases have been registered during the period of inclusion. Of these 451,825 are unique ED encounters of which suspected infection was registered in 60,316. Sepsis were present in 28,472 and 8027 were defined as septic shock.

Table 4 Definitions Used in the Database of Community: Acquired Infections in Eastern Denmark 2018–2022

		Criteria
A	Suspected infection (Presence of criteria 1 and/or 2)	1: Clinician obtained any specimens for culture from any anatomic site (irrespective of the result) or microbiological analyses 2: Administered any duration of antimicrobial therapy within 24 h after arrival
B	Suspected Sepsis (Presence of both criteria 1 and 2)	1: Clinician obtained blood culture (irrespective of the result) 2: Administered antimicrobial therapy within 24 h after arrival
C	Sepsis (Presence of both criteria 1 and 2)	1: Suspected Sepsis (Definition B) 2: SOFA score of ≥2 points within 24 h of admission (Table 2).
D	Septic Shock (Presence of both criteria 1 and 2)	1: Sepsis (Definition C) 2: Vasopressor to maintain MAP ≥65 mmHg and Serum lactate ≥18 mg/L, in the absence of hypovolemia

Abbreviations: MAP, mean arterial pressure; SOFA, Sequential Organ Failure Assessment.

Informatics

By joint venture cooperation between authors JGH/TS and the Capital Region of Denmark with EPIC/Health Data (Danish: *Sundhedsdata*) an electronic data warehouse has been established based on a user-friendly Microsoft Azure cloud computing platform (Danish: *Forskerplatformen*) in which EMR data – from Danish registries (DCRS and DNPR), laboratorial (registered with the use of the International System of Nomenclature, Properties, and Units (the NPU system) – and microbiological results (Laboratory information system at the Department of Clinical Microbiology, Herlev), medication (categorized according to the Anatomical Therapeutic Chemical Classification System, ATC codes) and vitals (triage and early warning score (EWS) data) are merged and made accessible for data and biostatistical analyses. Continuous update of data is possible after obtaining proper approvals.[49]

Variables

The database includes several descriptive variables, clinical and time dependent variables, in addition to outcome indicators (Table 5).

Table 5 Variables Included in Database of Community Acquired Infections and Sepsis in Eastern Denmark (DCAISED)

Category	Description	Data Variable/Source[b]
Demographic variables	Civil registration number Age Gender Date of Birth Municipality of Residence Migration status Vital status	DCRS
ED contact	Place of Admission (Department, Hospital, Region) Date and time of hospitalization Date and time of first triage Reason for admission Referral type (referred by GP, ambulance, self-referral)[a]	DNPR
Diagnoses	Inpatient and outpatient diagnosis Main diagnosis from the index hospital contact Discharge diagnoses.	DNPR
Vital parameters	Systolic blood pressure (mmHg) Diastolic blood pressure (mmHg) Heart rate (beats/min) Saturation (%) Altered mental status (GCS/AVPU) Temperature (C)	Triage/EWS
Laboratory variables	Hemoglobin (g/L) Leukocytes (× 10^9/L) Neutrophils (× 10^9/L) Lymphocytes (× 10^9/L) Thrombocytes/Platelets (× 10^9/L) CRP (mg/L) Creatinine (μmol/L) Bilirubin (μmol/L) INR Lactate (mmol/L)	NPU system

(*Continued*)

Table 5 (Continued).

Category	Description	Data Variable/Source[b]
Microbiological variables	Blood cultures	Microbiological laboratory information system (Site; Herlev)
	Sampling time	
	Number of positive blood culture bottles	
	Number of blood culture bottles inoculated	
	Bacterial/fungal species and results from antimicrobial	
	Susceptibility testing	
	Respiratory samples:	
	Gram stain and culture results, including species and antimicrobial susceptibility testing	
	PCR results for atypical bacterial pathogens (*Legionella* spp., *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Chlamydia psittaci*)	
	PCR results for respiratory viruses (SARS-CoV-2, influenza virus A and B, adenovirus, parainfluenza virus, respiratory syncytial virus, human metapneumovirus, and rhinovirus)	
	Urine:	
	Culture results, including species and antimicrobial susceptibility testing	
	Urine antigen testing (*Legionella pneumophila, Streptococcus pneumoniae*)	
	CSF	
	Gram stain and culture results, including species and antimicrobial susceptibility testing	
	PCR results from syndromic panels	
	Other fluids and tissues	
	Culture results, including species and antimicrobial susceptibility testing	
	Swabs	
	Anatomic localization	
	Culture results, including species and antimicrobial susceptibility testing	
Medication	Known medication upon ED arrival	ATC codes
	Medication administered during admission/hospitalization	
	Time of prescription	
	Medication dispensed	
	Indication, strengths, volume, frequency	Unique code/unifier
Computational covariates	Comorbidity	ICD-10
	Cerebrovascular disease (ICD-10: I60–I69; G45; G46)	
	Dementia (ICD-10: F00–F03; F05.1; G30)	
	Chronic pulmonary disease (ICD-10: J40–J47; J60–J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3)	
	Connective tissue disease (ICD-10: M05; M06; M08; M09; M30; M31; M32; M33; M34; M35; M36; D86)	
	Ulcer disease (ICD-10: K22.1; K25–K28)	
	Mild liver disease (ICD-10: B18; K70.0–K70.3; K70.9; K71; K73; K74; K76.0)	
	Diabetes I and II (ICD-10: E10.0, E10.1; E10.9, E11.0; E11.1; E11.9)	
	Hemiplegia (ICD-10: G81; G82)	
	Moderate-to-severe renal disease (ICD-10: I12; I13; N00–N05; N07; N11; N14; N17–N19; Q61)	
	Diabetes with end organ (ICD-10: E10.2–E10.8; E11.2–E11.8)	
	Any tumor (ICD-10: C00–C75)	
	Leukemia (ICD-10: C91–C95)	
	Lymphoma (ICD-10: C81–C85; C88; C90; C96)	

(*Continued*)

Table 5 (Continued).

Category	Description	Data Variable/Source[b]
	Moderate-to-severe liver disease (ICD-10: B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85) Metastatic solid tumor (ICD-10: C76–C80) Acquired immune deficiency syndrome (ICD-10: B21–B24) CCI (ICD-10 coded hospital discharge diagnoses from the previous 10 years) Low level of comorbidity (0) Moderate level of comorbidity (1–2) High (>2) level of comorbidity SOFA score Computed from six variables (each representing an organ system). Each organ system is assigned a point value from 0 (normal) up to 4 (severe degree of dysfunction/failure) Ranges from 0 to 24 Site of organ failures Cardiovascular Renal Coagulation Hepatic CNS Respiratory	NPU/EWS/ATC NPU/EWS/ATC
Outcome	30-day mortality 90-day mortality 365-day mortality Length of entire hospital contact (course) ICU length of stay ICU 30-day mortality Prevalence (presence of and type of infection, sepsis, septic shock)	DCRS/DNPR ATC/ICD-10/microbiological laboratory information system

Notes: [a]Self-referral: Patients attending the ED on their own initiative (without a referral from a GP or brought in by ambulance/prehospital service. [b]Information from registries DCRS and DNPR are integrated in the electronic medical journal (EMS) provided by EPIC.

Abbreviations: ATC system, the Anatomical Therapeutic Chemical Classification System; AVPU scale, "alert, verbal, pain, unresponsive"; CCI, Charlson Comorbidity Index Score; DCRS, Danish Civil Registration System; DNPR, Danish National Patient Registry; ED, emergency department; EWS, early warning score; GCS score, Glasgow Coma Scale; GP, general practitioner; ICU, intensive care unit; ICD-10 codes, International Classification of Diseases, 10th revision; CNS, central nervous system; NPU system, International System of Nomenclature; INR, (international normalized ratio), Properties, and Units; SOFA score, Sequential Organ Failure Assessment score; SBT, systolic blood pressure.

Descriptive variables include baseline demographics: age, gender, municipality of residence, migration, and vital status. Inpatient and outpatient diagnosis as well as discharge diagnoses and a main diagnosis from the index hospital contact. Clinical time-dependent variables based on patient data upon ED arrival includes time and date of arrival, triage level and time of assessment by ED personal and physician, time of microbiological requisition for culture and time of positive culture, as well as time of laboratory to analyze requisitions, and initiation of empiric antimicrobial treatment. Clinical variables include vital values and signs at presentation to the ED and during the course of hospitalization; systolic and diastolic blood pressure, heart rate, temperature, oxygen saturation and respiratory frequency, as well as clinical judgment of consciousness in terms of AVPU ("alert", "voice responsive", "pain responsive", "unresponsive") scale or GCS (Glasgow Coma Score). Laboratory variables for the entire hospitalization are included and consist, but are not limited to arterial blood gas variables (including lactate), hematological variables (eg hemoglobin, leucocytes, thrombocytes), inflammatory markers and acute phase proteins (eg C-reactive protein, procalcitonin) and organ-specific variables (eg creatinine, bilirubin). The laboratory variables and results are registered including the unique identification codes of the laboratory and the specific requisitioner. Microbiological variables include culture results from blood, urine, lower respiratory tract, cerebrospinal fluid (CSF) and other anatomical sites (eg pleural fluid, ascites, swabs from abscess cavities and skin lesions). Culture results include bacterial/fungal species and

antimicrobial susceptibility patterns used to determine rates of appropriate therapy. In addition, specific polymerase chain (PCR) results are included (eg influenza virus and SARS-CoV-2 from the respiratory tract) as well as serological tests.

Additional variables include medication administered upon inclusion and during the course of hospitalization. Special emphasis is on antimicrobial treatment (including antibacterials, antifungals, and antivirals), treatment with intravenous fluids and volumes administered, as well as vasopressor agents (ATC codes) (Table 5).

Computational covariates include Charlson Comorbidity Index (CCI), SOFA score, number and site of organ failure. CCI as a proxy for comorbid illness, are included for each enrolled patient upon index contact and computed based on diagnoses up to the previous 10 years before index contact.[50] The SOFA score is computed from six variables, each representing an organ system (eg pulmonal or circulatory) for each included patient upon index contact. Each organ system is assigned a point value from 0 (normal) up to 4 (severe degree of dysfunction/failure) and ranges from 0 to 24 (Table 2).[12,51] The individual organ systems and presence of degree of dysfunction/failure are based on laboratory variables, vasopressor administration and vital values as described above.

Outcome indicators include occurrence of infections, foci, severity of infections (localized, versus systemic) mortality proportions at 30, 90, and 365 days from index date. Number of organ failures based on SOFA score and ICU care during hospitalization. In case a patient has multiple ED events with the event of interest within the study period, only the first event is included for the outcome indicators.

Algorithm development and validation of definitions used for this cohort is planned as future objectives for investigation.

Completeness, Missing Data, and Data Validity

All patient data stored in the EMR software *Sundhedsplatformen* in the clinical setting is available in the database. The strength of this database is the detailed clinical data from all EDs and inpatient wards from all hospitals in the Capital and Zealand Region of Denmark. These two regions together account for half of the Danish population. The EMR data is independently recorded and based on data from the public Danish health care system (free tax-paid for all Danish residents), which is almost complete[41,43,45] whereby the risk of selection bias and loss to follow-up is regarded as minimal. Moreover, the catchment area is well-defined in this part of Denmark bordered by the ocean due to the geographical characteristics (Figure 1).

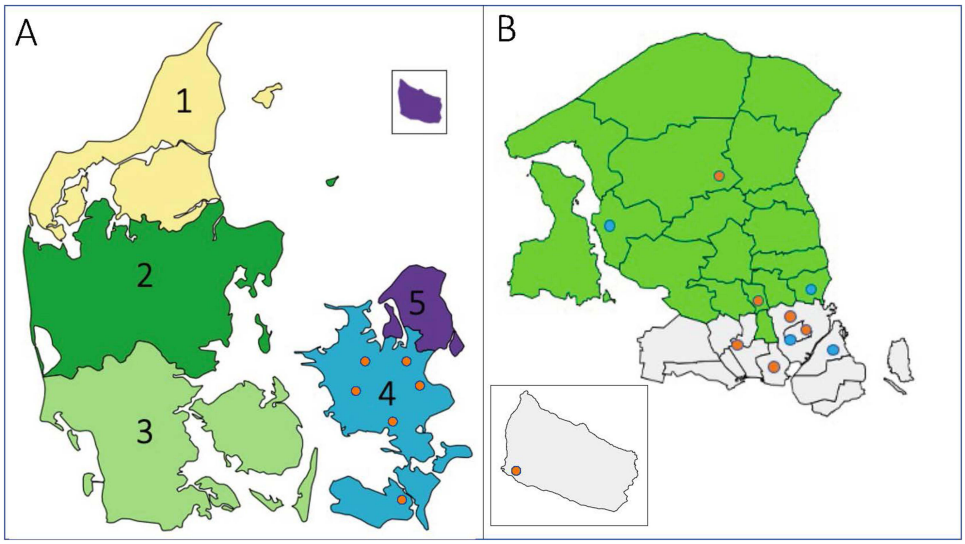

Figure 1 (**A**) Overview of the five regions of Denmark (Total population ~ 5.8 million). (1) North Denmark Region (population ~0.6 million), (2) Central Denmark Region (population ~1.3 million), (3) Region of Southern (population ~1.2 million) Denmark, (4) Zealand Region (population ~0.8 million) and (5) Capital Region of Denmark (population ~1.8 million). The DCAIED database comprise all adult ED visits of patients (age ≥18 years) in whom an infection is suspected, and the background population are inhabitants living in Regions 4 and 5 (eastern part of Denmark). The EDs provide all together 24-h acute emergency care for 2.6 million inhabitants. Red dots represent EDs in the Zealand region. (**B**) Overview of the Capital Region of Denmark. EDs are represented by red (24-h acute emergency care) and blue dots (day-time acute emergency care). The municipalities highlighted by green color, and the EDs situated within, are served by the Department of Clinical Microbiology, Herlev.

The vital and laboratory parameters are registered prospectively for routine documentation and not for research purposes. We argue that laboratory parameters are missing in a systematic, nonrandom fashion as biochemical and microbiological samples are retrieved only when a health-care worker deemed it appropriate based on a clinical judgment.

Currently, microbiological data are available for North Zealand Hospitals and Herlev and Gentofte Hospital which are served by the same Department of Clinical Microbiology at Herlev Hospital (see Figure 1 for geographical location). It is planned to establish future cooperation's with the other clinical microbiological departments in the regions. Electronic medical records are well implemented in all Danish Hospitals and EDs. Initiatives to expand the present database by a similar data-infrastructure application from the western part of Denmark (Figure 1) are relevant for research purposes on a national and international level. Presently, the technological solution for this infrastructure has yet to be established, as the software applications and companies hosting the electronic medical records across the regions in Denmark are different. Validation of data completeness and variables in the database is ongoing.

Permissions and Access for Other Researchers

The data retrieval is approved by the Danish Health and Medicines Authority (DHMA) (record number: 3-3013- 2976/1) and the legal department of the Capital Region of Denmark (record number: P-2019-626). We have sought a waived informed consent since the collection of data does not carry any risk for the involved patients. Permission from an ethical committee and patient consent is therefore not required for this type of database in Denmark. All data are handled according to national and regional laws and in compliance with relevant data protection and privacy regulations. Data are made available in an anonymized form to accomplish the DHMA regulations.

Suggestions for studies and collaboration can be directed to the corresponding author JGH at jon.gitz.holler@regionh.dk and to author TS at theis.skovsgaard.itenov@regionh.dk. Studies and ideas for collaboration will be evaluated according to feasibility, timeliness, and clinical relevance, among others, together with relevant representatives from the emergency departments, and hospitals in the Capital and Zealand Region of Denmark. Data on the individual-level will not be made publicly available in accordance with Danish law. Multidisciplinary collaborations with other Danish and international researchers are encouraged.

Perspectives on Infection and Sepsis Research and Reported Outcomes

Population-level epidemiological estimates of the incidence of infections and sepsis are largely based on administrative databases (hospital discharge codes, etc) (Table 3). These data are often advantageous in the context of large-scale epidemiologic research, as the data acquisition is less resource demanding. Studies based on administrative databases coherently describe an increasing incidence of sepsis during the past 30 years[18,19,23–25,28–31,33,35,36,38,52] and declining mortality rates.[19,24,25,29,31,33,35,36,38,52] However, administrative data is susceptible to bias by different thresholds and variability in diagnosing and coding practices of infectious diseases, sepsis and organ failures. Despite of similar trends in outcome, Gaieski et al[31] found great variations in incidence and mortality estimates, based on four different administrative coding definitions.[18,19,25,26] Moreover, changing coding practices over time caused by changing definitions of sepsis, increased focus (eg Surviving Sepsis Campaign),[53] as well as reimbursement motivations in some countries all add to possible discordance in the reported estimates and challenges comparability of outcomes.

In contrast, clinical databases, as a data source for epidemiological studies, commonly include patients in a prospective protocolized manner, based on consistent and well-defined clinical inclusion criteria. The latter contrasts to administrative definitions based on less precise discharge codes. However, due to the critical nature of severe infections and presence of organ failure, most studies based on clinical databases have only included patients in the ICU setting and epidemiological estimates therefore are prone to selection bias. Studies based on this selection, prior to the consensus definition of 2016, report incidences of severe sepsis treated in the ICU of 46 to 95 per 100,000 population[21,22,24,27] and mortality estimates between 28% and 48%.[21,22,24,27,32] In the large epidemiological study by Kaukonen et al[32] the proportion of sepsis admissions (relative to the total ICU admissions) increased from 7.2% to 11% from 2000–2012, whereas mortality rates decreased from 35.0% to 18.4%. In the study of similar size by Harrison et al[24] hospital mortality for admissions with severe sepsis decreased from 48.3% in 1996 to 44.7% in 2004, but the total number of deaths increased with an estimated increase in incidence of severe sepsis of 46 in 1996 to 66 in 2003 per

100,000 and an associated number of hospital deaths per 100,000 population rising from 23 to 30. Due to the heterogeneity in epidemiological estimates and uncertainty about the accuracy of the reported trends, Rhee et al[4] explored trends in incidence of sepsis and related mortality or discharge to hospice, based on clinical sepsis surveillance definition (sepsis-3) vs ICD-9-CM codes (claims data) and found outcomes based on the clinical surveillance definition stable between 2009–2014. Authors also stated that clinical data likely provide more objective estimates than claims-based data for sepsis surveillance.[4]

Comprehensive meta-analysis of observational and randomized controlled trials (RCTs) delineate great heterogenicity in studies included and questions the decline in mortality rates, as described by administrative data.[54–57] In the study by Luhr et al[56] 44 RCTs were included and analyzed in the usual care arm during the period 2002–2016. They found a declining trend in 28-day mortality in severe sepsis and septic shock during the years 1991–2013, however, the trend was nonsignificant when controlling for severity of illness. In the study by Vincent et al exploring mortality outcome among ICU RCTs, significant heterogeneity was observed.[57] Similarly, de Grooth et al[54] found significant heterogeneity in the control groups of mortality rates, based on 65 septic shock RCTs and a nonsignificant decline in mortality rates 2006–2018. Lately, Bauer et al[55] found a pooled septic shock estimate of 34.7% based on 170 studies, and mortality rates from RCTs were below previous prospective and retrospective cohort studies. A statistically significant decrease of 30-day septic shock mortality was found between 2009 and 2011, but not after 2011. Whether significant epidemiological trends in outcomes of sepsis and septic shock exist is thus still a controversy and population-based estimates are of high relevance.

The number of patients presenting to EDs is growing in many countries with crowding issues as a consequence.[58] In Denmark crowding has become a problem in the ICUs and internal medicine departments and it is expected to be a concern in Danish EDs in the near future.[58] With an increasing population presenting to the ED, of which a substantial proportion are elderly comorbid, and often critically ill patients, the acute medical personnel and health care decision-makers seem to face a major challenge. As sepsis and septic shock are common and severe clinical entities, and likely underreported in Denmark,[8] epidemiological characterization of community acquired infections requiring hospital referral, sepsis and septic shock is of importance to identity the burden of disease and characterize the population of interest in the ED.

Furthermore, the present database extends the period before and during the COVID-19 pandemic. Register-based studies have delineated a decrease in hospitalization among non-COVID-19 disease groups during lockdown periods due to governmental mitigation strategies, whereas overall mortality rate ratios were higher between lockdown periods for non-COVID-19 respiratory diseases, cancer, pneumonia, and sepsis.[59] Authors highlight the study limitations in clinical details on disease severity as well as comorbidities of people admitted to hospital in analyses of mortality. Due to the granular individual-level clinical data and longitudinal surveillance in the present database, it is possible to further delineate and address, potential confounding factors by examining pre- and post-pandemic outcome rates for specific conditions and community-acquired infectious diseases within the present cohort.

Recently, perpetual observational studies have been proposed as a study design to continuously collect clinical and demographical data for infectious disease entities.[60] In our setting, the retrospectively available detailed clinical data results in a similar database based on routinely collected data without the need to enroll patients and thereby avoiding bias.

In all respects, Denmark is a perfect setting for this kind of population-based studies. The available detailed clinical data from the Capital and Zealand Region of Denmark, enables large-scale, precise, and detailed epidemiological research on these clinical conditions.

Conclusion

The Database of Community Acquired infections in Eastern Denmark is a new database established by data from EMR records provided by the software *Sundhedsplatformen* including all adult ED hospital contacts in the Eastern part of Denmark with the purpose of conducting large-scale epidemiological research on community-acquired infections requiring hospital referral. The database includes a large cohort, with granular data, which gives detailed and precise research opportunities on different aspects of severe community-acquired infections and sepsis. It is planned to expand, improve, and validate the data completeness.

Abbreviations

AVPU, alert, verbal, pain, unresponsive; CCI, Charlson Comorbidity Index; CSF, cerebrospinal fluid; CPR, civil registration number; ED, emergency department; DHMA, Danish Health and Medicines Authority; GCS, Glasgow Coma Score; EMR, electronic medical records; ICU, intensive care unit; IQR, interquartile range; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; MAP, mean arterial pressure; MEWS, Modified Early Warning Score; NEWS, National Early Warning Score; qSOFA, quick Sequential Organ Failure Assessment; RCT, randomized controlled trial; SEPSIS-3, The Third International Consensus Definitions for Sepsis and Septic Shock; SIRS, Systemic Inflammatory Response Syndrome; SOFA, Sequential Organ Failure Assessment.

Disclosure

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